**REMARKS**

Claims 2, 4-11 and 50-54 are pending and are the subject of the office action mailed February 10, 2005. In the amendment above, claims 61-65 have been added. Claims 61-65 are fully supported by the specification as filed and accordingly do not introduce new matter.

Claims 2, 4-10 and 50-53 remain rejected under 35 USC 102(b) as being anticipated by Wiley (Immunity, 1995). The examiner also rejected claim 2, 4-11 and 50-54 under 35 USC 102(b) as being anticipated by US patent 5,763,223 (Wiley patent). Applicants respectfully traverse both rejections.

Applicants' findings, as described in the instant application, reveal the Apo-2 ligand structure as being the first example of metal binding-mediated trimerization of a cytokine. At the time of filing the instant application, ***none*** of the other structurally characterized members of the TNF family had been found to have metal-binding sites. Accordingly, it was unexpected to find that Apo-2 ligand polypeptides are coordinated in the form of trimers by way of a metal-binding site, in particular by way of a zinc binding site at position Cys230 in the Apo-2 ligand polypeptide sequence structure.

The references cited by the examiner do not teach each and every element of the claimed formulations, either expressly or inherently. The particular portions of the Wiley references cited by the examiner do not teach or suggest to one skilled in the art that effective amounts of zinc be utilized to stabilize Apo-2 ligand trimers in a formulation. This was not and could not have been appreciated prior to the present invention because it was not known in the art that TNF ligand family members bound metal ions such as zinc or that the biologically active trimer forms of such ligands could be coordinated and stabilized by a metal ion such as zinc. Indeed, those skilled in the art routinely used other means to form and stabilize trimeric forms of TNF ligand family members, such as through the use of leucine zipper molecules. The Wiley

references do not describe any particular aspects of monomer, dimer, or trimer forms of the Apo-2 ligand or how a formulation of Apo-2 ligand can be prepared to optimize stabilized, trimeric forms of the protein.

It is believed that Claims 61-65 added in the above amendment are also not anticipated by the Wiley references. Unlike the particular glycosylated and epitope-tagged forms of TRAIL (amino acids 95-281) cited by the examiner as having been prepared by Wiley in Tris buffer, claims 61-65 are directed to formulations of non-glycosylated Apo-2 ligand polypeptide which consist of the recited sequence structures and as such, are not linked to any heterologous amino acid sequences such as leucine zipper sequences or epitope tag sequences.

Respectfully submitted,
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